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DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date July 23, 1990

From Senior Scientific Advisor to the Director, NIEHS
Research Chemist

Subject Submission of Comments for the Request to Use Additive, MMT, in Gasoline

To Mary T. Smith
Field Operationa nd Support Division
U. S. Environmntal Protection Agency

The following information is submitted to the Air Docket for the U. S. Environmental Protection Agency in response to Federal Register Notice (Volume 55, Number 108/Tuesday, June 5, 1990/page 22947 [FRL-3784-9]) requesting waiver of the prohibition against the introduction to commerce of melthylcyclopentadienyl manganese tricarbonyl (MMT) as an additive to unleaded gasoline. The National Institute of Environmental Health Sciences (NIEHS) has reviewed information on the toxicity of MMT and manganese and offers this review to EPA for their consideration in evaluating the waiver application.

This submission is from the Office of the Senior Scientific Advisor to the Director, NIEHS and identifies critical biomedical issues that need to be considered in arriving at a decision on the waiver request. If there are questions on any of this material or if copies of the references cited are needed, please contact us.

Kathryn R. Mahaffey, Ph.D.
Research Chemist

James R. Fouts, Ph.D.
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Attachment

STATEMENT

The following information is submitted in response to a notice published in the Federal Register (Vol. 55, No. 108, Tuesday, June 5, 1990, page 22947 [FRL-3784-9] on a request for waiver of the prohibition against the introduction into commerce of certain fuels and fuel additives set forth in section 211(f) of the Clean Air Act. The application by Ethyl Corporation (Ethyl) seeks a waiver for the gasoline additive, methylcyclopentadienyl manganese tricarbonyl (MMT), an octane enhancer, commercially labeled as HITEC 3000, to be blended in unleaded gasoline resulting in a level of 0.03125 gram manganese per gallon of gasoline. The National Institute of Environmental Health Sciences has reviewed the biomedical literature on the adverse effects to human health of exposure to elevated concentrations of MMT and manganese. The toxicity of MMT is discussed below. Because MMT following combustion becomes predominantly manganese oxides, a discussion of manganese toxicity is presented separately. Manganese is both a required nutrient and a toxic element depending on the route, duration and extent of manganese exposure, as well as the susceptibility of the person exposed. Adverse health effects occurring in manganese intoxication are described more fully below.

The following effects on health associated with addition of MMT to gasoline have been identified as critical issues to be considered in response to Ethyl's request for waiver:

* Toxicity of MMT Following Dermal Exposure: MMT is readily absorbed dermally and can be neurotoxic.

There are a number of situations in which nonoccupational dermal exposures to gasoline occur. The number of persons with dermal exposure to MMT is impossible to estimate with accuracy, but can be conservatively projected to be millions of individuals yearly. Examples of routine exposure include:

* Skin contact with gasoline in filling lawnmowers and garden equipment, fueling boats, and occasional spills when fueling automobiles.

* Skin contact with gasoline used as a household degreasing agent; e.g., cleaning hands following repair work, cleaning bicycle chains.

* Exposure of children who accidently spill gasoline on their skin, but do not ingest gasoline: These children rarely come to the attention of emergency medical personnel.

* Manganese at high exposures produces pulmonary symptoms and at far lower exposures contributes to the prevalence of pneumonia and bronchitis in the general population (World Health Organization, 1980; Section 9.2).

* Neurotoxicity of Manganese: Manganese is a well-recognized human neurotoxin producing clinical neurological symptoms closely resembling Parkinson's Disease. As are other disorders involving the extrapyramidal tract, this Disease is characterized by abnormality in gait, movement, and balance. The time-course of development of this disorder, the relationship of environmental dose of manganese and internal dose of manganese associated with this condition either are not known or are highly variable from person to person.

The U. S. Environmental Protection Agency (EPA) (1984) has previously determined in the "Health Assessment Document for Manganese" that an adequate cohort investigation in human subjects to identify time-course, dose-response/effect to manganese does not exist. EPA (1984) also has described the inadequacies of primate studies reported in the scientific literature that evaluate time-course, dose-response/effect with neurotoxicity as the endpoint. To the best of our information, additional studies that would fill this gap in knowledge have not been published since 1984. The NIEHS believes that until this research need is met, granting the waiver requested by Ethyl should be delayed or denied.

* Manganese can promote neurological disease at doses lower than those that produce overt signs and symptoms of Parkinson's Syndrome: Biochemical analysis of central nervous system tissue from nonhuman primates and humans poisoned by manganese show that manganese causes a reduced concentration of dopamine (a chemical used by the nervous system in communicating from cell to cell). These findings implicate the dopaminergic system in the extrapyramidal manifestations of chronic manganese poisoning (World Health Organization, 1980).

Typically, humans have substantial reserve capacity in the nervous system. Generally damage to approximately 80% of the cells and a reduction of the neurotransmitter levels to under about 20% of their typical concentration is necessary before clinical signs and symptoms of Parkinson's Disease are identified (Archibald and Tyree, 1987). A review of literature by Jellinger (1987) indicated that in Parkinson's Disease the loss of pigmented nigral neurons ranged from 63% to 84% in clinically diagnosed disease.

As noted above, manganese exposure at high doses has produced clinically obvious neurological disease. Given the extent of cell damage and neurotransmitter depletion necessary prior to the onset of overt disease, manganese can produce

substantial damage to the extrapyramidal tract prior to the observation of signs and symptoms of clinical disease. Other factors also result in reduction of the number of neurons in this system and depletion of neurotransmitters including dopamine. These include: genetic variability in the rate of death of these cells, loss of neurons with increasing age, concurrent disease conditions, other environmental agents, and various pharmaceutical agents.

Because of the "silent" character of these losses prior to the onset of signs and symptoms, effects of manganese could occur at concentrations far lower than produce clinical disease. Although these differences produced by manganese would alone not produce obvious disease, these changes added to other factors [e.g., aging, genetic variability (Price et al., 1987; Lai et al., 1987)] could contribute to premature onset of neurological disease. Manganese may accelerate the aging process of the dopaminergic system through enhanced autoxidation of dopamine (Donaldson et al., 1980).

* High Retention of Manganese among Infants and Young Children: Manganese exposure early in life (infancy and early childhood) may predispose to development of neurological disease later in life. Infants do not have the capability of limiting gastrointestinal absorption and excretion to the same extent as do adults. Based on extrapolation from animal data, the very young could accumulate manganese in the central nervous system. Use of manganese-enriched infant formulas has been associated with learning disability among children (Collipp et al., 1983).

* Wide Variation in Individual Susceptibility to Manganese Toxicity: Individual susceptibility to manganese toxicity appears to be highly variable given the very wide range of exposures associated with the clinical cases reported.

Manganese absorption is greater in iron-deficient individuals because gastrointestinal absorption of manganese appears to utilize proteins that transport iron across the gastrointestinal barrier. A disease of iron metabolism (idiopathic hemochromatosis) exists in which iron is over-absorbed to the extent that the iron excess proves fatal. Manganese shares this absorption pathway. Excessive absorption of manganese could occur which may accelerate the aging process of the nervous system.

* Susceptibility of the Population to Neurodegenerative Disease: The demographic profile of the United States population has changed, resulting in a population that is older on the average than at any previous time in our Country's

history. This longer life span may permit time for the expression of clinical manifestations of neurological disorders that occur with the aging process. The petition to permit increased use of a known neurotoxin to a product as widely dispersed as gasoline is a request that must be very carefully evaluated to avoid a future epidemic of neurological disease.

* Manganese is Required in the Diet: Manganese is a required nutrient in all species investigated. Based on literature reports of the quantities of manganese consumed in human diets, it appears that humans tolerate dietary intakes of approximately 6 to 9 milligrams of manganese per day without clinically-obvious disease.

* Contribution of MMT to Manganese in Airborne Fine Particles and to Particulate Fallout Is Unclear: The petition to EPA for addition of MMT to gasoline would add 31 milligrams of manganese per gallon of gasoline. Data in the petition for waiver indicate approximately 5 percent of the 31 milligrams of manganese per gallon has been found, so far, to result in tailpipe emissions. The disposition of the remaining 95 percent is unknown. Release of the remaining 95% of this manganese to the environment will occur sooner or later. The fraction of the manganese not yet accounted for is approximately 29.5 milligrams of manganese per gallon of gasoline. This quantity of manganese is approximately the amount of manganese that a person would consume in 10 days of diet (ranging from about 6 to 20 days of dietary manganese intake).

A substantial increase in the ratio of manganese/silicon in airborne fine particles attributed to use of a manganese-containing additive in leaded gasoline has been reported in California where MMT is used as a gasoline additive to leaded gasoline (Davis et al., 1988). It is unclear whether or not environmental build-up over several decades of using MMT in gasoline would compromise the neurological health of susceptible members of the population.

GENERAL DISCUSSION OF THE TOXICITY OF MMT AND MANGANESE

MMT

MMT is currently used in leaded gasoline under the trade mark "HiTEC 3000". The National Toxicology Program has previously prepared a profile on MMT in 1986, shown as Appendix 1.

MMT is highly toxic. The Registry of Toxic Effects of Chemicals (NIOSH) indicates that the rat LC50 by inhalation is 76 milligrams/cubic meter for 4 hours; by intraperitoneal injection the rat LD50 is 23 milligrams/kilogram body weight; by ingestion the rat LD50 is 50 milligram/kilogram body weight; and by skin the rabbit LD50 is 140 milligram/kilogram body weight.

Occupational exposures to MMT have occurred, and recommendations have been made to limit exposures. The American Conference of Government and Industrial Hygienists (ACGIH) has established a threshold limit value-time weighted average (TLV- TWA) of 0.2 milligrams/cubic meter (expressed as manganese). MMT is highly toxic by all routes of exposure: inhalation of vapors, ingestion of liquid and percutaneous absorption. The TLV-TWA for MMT carries a notation for "skin" indicating extensive dermal absorption. The TLV-TWA lists central nervous system toxicity as the primary site of action. The toxic responses in rodents and rabbits included: mild excitement, hyperactivity, tremors, severe clonic spasms, weakness, slow and labored respiration, occasional mild, clonic convulsions, and terminal coma (ACGIH, 1988). For comparison the TLV-TWA for tetraethyl lead, a well-established central nervous system toxicant, is 0.1 milligram/cubic meter.

Only one company, Ethyl, is known to manufacture MMT in the United States. Their process uses an enclosed system to reduce worker exposures. The greatest chances for exposure occur in transport and blending of the additive with fuels. The vapor pressure of MMT is sufficiently low that inhalation of vapors by people pumping "self-serve" gasoline would give very small exposures to MMT. As an additive to gasoline, the predominant possibility of MMT exposure is through contact with the skin and subsequent dermal absorption. This would occur when there are gasoline spills or if gasoline is used to clean the hands. Accidental ingestion of gasoline would also be a source of exposure to MMT.

MMT is unstable and rapidly decomposes in light. When the gasoline is combusted in an engine, over 99.9 percent of the MMT is burned. At the high temperatures of the internal combustion engine, the tetroxide (Mn_3O_4) is the principal component. Particle sizes are typically small, in the range of 0.2 to 0.4 micron as the mid-range of the products of combustion.

The quantities of manganese associated with the use of MMT can be calculated as follows: 31 milligram of Mn/gallon x 20 gallons per tank adds approximately 620 milligrams of Mn per tank of gasoline. Alternately, 31 milligrams Mn/gallon x 25 miles per gallon results in approximately 1.25 milligrams (or 1,250 micrograms) of manganese per mile.

Ethyl, as part of their petition for waiver, has estimated the amount of manganese which is exhausted from cars using 31.25 milligram Mn/gallon and EPA particulate sampling techniques described in Code of Federal Regulations 86.100-82, 86.111-82, and 86.112-82. These methods were designed primarily to measure diesel particulates. Studies of nine automobiles at 75,000 odometer miles indicated that these emitted approximately three to seven micrograms Mn/mile.

Clearly, this is a tiny fraction of the 1,250 micrograms of manganese that was in the gasoline. Apparently, Ethyl has not done the mass balance to determine where the manganese has been lost to the environment. Current theory is that the manganese plates onto the catalytic converter and the exhaust system. Alternate explanations include manganese lost as vapor or as very fine particles released into the environment.

A study on the origins of manganese in air particulates in California (Davis et al., 1988) reported a six-fold increase in the manganese/silicon ratio of airborne fine particles (under 2.5 micron) after major oil companies began adding an anti-knock compound containing manganese to leaded gasoline in 1985 or late 1984. The ratio of Mn/Si increased from about 0.005 in 1984 to approximately 0.03 in early 1986. This increase occurred in sites that receive substantial automobile traffic. Levels of airborne manganese and lead were often highly correlated at sites receiving automobile traffic; suggesting automobile vehicles as the source of manganese. Site apportionment of the manganese indicated vehicular emissions of manganese appear to account for a significant part of the total manganese at urban sites in Southern California. At sites remote from vehicular traffic, the contribution from vehicles was found to be smaller than from the earth's crust.

This increase did not occur for larger particles (diameter >2.5 micron and <10 micron. Upon inhalation fine particles are deposited deep in the lung and can be absorbed across the alveoli. The percent retention of manganese via this route is greater than from the gastrointestinal tract. The manganese on fine particles, absorbed via the lung, has greater bioavailability than manganese absorbed from the gastrointestinal tract.

The data submitted by Ethyl in their petition for waiver indicate that only about 3 to 7 micrograms per mile driven are emitted on particulates (presumably under 2.5 micron in size). This indicates that the vast majority of the manganese is lost somewhere in the engine, oil, catalyst, exhaust systems or is released to the environment. The California data indicate a

six-fold increase in the manganese-silicon ratio, attributable to vehicular origin. This information is difficult to reconcile with the data presented in the Ethyl petition.

The EPA should require that Ethyl conduct appropriate mass balance studies to determine where the manganese has gone. The possibility that MMT passes through the engine and exhaust system and is exhausted as a vapor containing MMT should also be considered. Although it would appear that these are very small quantities of manganese, when expressed as quantities of manganese added to leaded gasoline, the importance of the volume of the gasoline product becomes more apparent. Data from the paper of Davis et al., (Figure 3, page, 1154, 1988) show that approximately 55 tons of manganese in 1985 and approximately 69 tons of manganese in 1986 were added to leaded gasoline sold in California by major oil refiners. The impact of being unable to identify through mass balance the location of over 95% of such quantities is a matter of concern that must be addressed by the petitioner.

MANGANESE

Combustion of MMT in the engine produces various manganese oxides. The principal component is the teroxide (Mn_3O_4) indicating high temperature combustion. The biotoxicity of manganese, as for most other metals, depends on: 1) route of exposure, 2) particle size, and 3) the chemical species of manganese, i.e., valance, cations present in the manganese compound.

The ACGIH TLV-TWA for manganese tetroxide is 1 milligram/cubic meter (expressed as Mn) which was established in industries in which manganese fumes were generated in the pouring and casting of molten ferromanganese. The TLV-TWA for manganese is 5 milligram/cubic meter. The biotoxicity is related to particle size with inhalation of manganese fume producing the most severe toxic effects. The central nervous system and the pulmonary system are the primary target organs.

MANGANESE TOXICITY

Both chemical pneumonitis and neurological damage occur with manganese exposure. The pulmonary symptoms include edema and suceptibility to pneumonia (Kimbrough et al.,.1989). Roels et al.,(1987) reported acute bronchitis was about twice as prevalent, 38 percent vs. 19 percent, in manganese workers compared with controls.

HUMAN NEUROTOXICITY

The neurotoxicity of manganese has been recognized for over 150 years with the earliest cases identified by Couper in 1837 among workers refining manganese ores. Numerous reviews of this condition include those by Abbott, 1987; Barbeau, 1984, and Donaldson, 1988. Exposure to high concentrations of manganese produces a clinical condition that is virtually identical to Parkinson's Syndrome. Signs and symptoms include: psychoses, emotional instability, rigidity of muscles, disorders of gait, and mask-like facial expression.

The neurological and behavioral toxicity of manganese have been reviewed previously by EPA and described in the "Health Assessment Document for Manganese", Final Report, 1984. The summary of the neurotoxicity section (page 6-22) concludes the following: "An important effect of chronic exposure to manganese is the chronic manganese poisoning resulting from occupational exposures to manganese dusts after only a few months of exposure, although other cases develop only after many years. Earlier studies report advanced cases of manganism (in various miners), but more recent studies report cases showing neurological symptoms and a few signs where the exposure was at much lower concentrations. Whether this reflects different chemical form and particle size of the inhaled manganese, a straight dose-response effect, or inconsistencies in clinical examinations is not clear." The final paragraph of the summary (page 6-23) states: "in order to obtain definitive dose response data, a cohort study is needed, including documented clinical examinations, more accurate exposure characterizations as well as exposure data on individuals. All members of the cohort should be followed for neurological signs for, at least, 20 years and members lost to follow up should be clearly reported."

Several reports of manganese neurotoxicity in human subjects have been published since 1984. Studies that have reported signs and symptoms of extrapyramidal tract disorder without full Parkinsonian symdrome include the following:

Ferraz et al. (1988) who reported two cases of Parkinsonian syndrome in two young agricultural workers exposed to the fungicide Maneb (manganese ethylene-bis-dithiocarbamate), and identified a significantly higher than expected prevalence of extrapyramidal tract neurobehavioral disorders among other workers exposed to Maneb.

Sano et al. (1982, English abstract only; full text in Japanese) contrasted the incidence of subjective symptoms of chronic manganese exposure among 162 retired miners and ore

grinders with those of 124 people living in the same region of Japan. The incidence of emotional instability, psychomotor irritability and neurological abnormalities was higher in the exposed group and increased with the period of exposure to manganese dust. Twenty-eight percent of the workers reported the subjective symptoms while they were employed, but 45 percent of them reported these as late as six years after they retired. Among the retired workers, 3.1% has Parkinsonism, 1.9% showed symptoms of hemi-Parkinsonisms, 9.3% showed neurological symptoms including mask-like facial expression, gait imbalance, slurred speech and impaired fine movements. Forty-five percent of the exposed group recognized these abnormalities as continuing for at least five years after they had left the contaminated worksite. Pneumoconiosis was present in 39% of the retired workers.

Szeliga-Cetnarowska (1987, English abstract only, full-text in Polish) reported diminished peripheral nerve conduction rate in motor and sensory fibers of three peripheral nerves among 57 workers that experienced manganese dioxide exposure in a flux division. The electromyogram of these workers exhibited concurrent denervation with changed motor conduction in approximately 37% of the manganese-exposed workers.

Animal Studies of Neurotoxicity

Animal models of chronic nervous system effects of manganese have not been duplicated successfully in any experimental animal except higher monkeys and then only after inhalation or intraperitoneal administration (Goyer, 1986). Several studies on effects of manganese in nonhuman primtes have been published in the literature. The EPA evaluation of manganese in 1984 noted (page 6-28): "Primates are a better experimental animal than rodents for studying the neurological manifestations of manganese intoxication. Several studies with manganese dioxide-exposed monkeys have been performed (Mella, 1924; Neff et al., 1969; Pentschew et al., 1962; Suzuki et al., 1975), but all were conducted under inadequate experimental conditions (small number of animals were exposed to large, widely spaced doses of manganese by non-natural routes) . . .However, these exposures did consistently product extrapyramidal symptoms (excitability, intentional tremors, rigidity in the extremities) and/or histological lesions (damage to the putamen, caudate, subthalamic nucleus, and pallidum) that were remarkably similar to those described in cases of human manganism."

The existing studies on the neurotoxicity of manganese in nonhuman primates are inadequate to assess dose-response, dose-effect relationships. There are, however, a number of studies on the cellular effects of manganese excess.

MANGANESE BIOKINETICS

Manganese and its compounds are absorbed via the lungs and gastrointestinal tract. Manganese is initially accumulated in the lung if the exposure is via inhalation, and in the liver if the exposure is via ingestion. From these tissue deposits manganese can be transferred to the nervous system.

Inhalation

As with many other metals, pulmonary absorption of manganese depends upon particle size, rate and concentration of the exposure, and the oxidation state of the cation. Absorption via the lung is highly dependent upon particle size with particles in the 2-4 micron range reaching the alveoli. The manganese burden in the lung can be slowly transferred to other tissues.

Retention of manganese following inhalation exposure has been investigated in nonhuman primates and human subjects. Long-term manganese retention in the central nervous system can result from acute exposure. For example, Newland et al. (1987) exposed Macaque monkeys to trace amounts of $^{54}MnCl_2$ for 30 minutes via inhalation. Although the half-time for removal of the acute dose was less than a day, about 5 to 10% of the initial deposited dose remained in the lung 6 months after exposure. Measured radioactivity in the head peaked at approximately 40 days and then declined. Nonetheless, more than one year after the initial 30-minute exposure, measurable levels of the original manganese were detected in the head. The report of very long biological half-times for brain manganese following inhalation raises the possibility that long-term exposures to even low levels of manganese will cause significant accumulation of manganese in the brain.

Ingestion

Manganese is also absorbed from the gastrointestinal tract. Absorption depends upon: 1) particle size of the manganese compounds, 2) valence of the manganese, 3) other components of the diet, 4) developmental stage of the subject, 5) iron-status of the subject, and 6) individual factors.

Manganese is absorbed into mucosa cells throughout the small intestine (Kies, 1987). Manganese appears to be mainly absorbed as Mn^{++}. In the adult absorption is typically under 10% and is not under close homeostatic control. Excretion of manganese into the bile and pancreatic juice appears to be, at least, as important as absorption in determining body-burden of manganese. Gastrointestinal absorption is regulated in the adult. Although

typical subjects absorb under 10% of ingested manganese, iron-deficient subjects absorb over 40% of ingested manganese (Sandstrom et al., 1986). Female subjects are thought to be more susceptible to the toxic effects of manganese, possibly reflecting a greater prevalence of low iron-status among females.

During the neonatal period and early in infancy, manganese is absorbed at substantially higher percentages than in the adult. Young animals absorb a higher percent of ingested manganese. The specific form of manganese produced by combusion of MMT, manganese tetroxide, has been found to be absorbed and retained to a greater extent than other manganese oxides/salts by young rats (Rehnberg et al., 1980). The chemical form of the manganese salt has been reported not to affect the percent absorption in the weanling rat (King et al., 1979).

Cahill et al., (1980) evaluated the influence of age of the animal, manganese compound and dose on the retention of manganese by the young rat. At low doses (10 to 25 micrograms/animal) manganese retention (as the percent of the ingested dose) of the chloride or oxide was equivalent. However, at the higher dose manganese chloride was retained to a much greater extent; 12-times greater than the oxide at the highest dose. Retention of manganese was also age-dependent. At 10 days of age, gastrointestinal retention of manganese by infant rats was 22%.

The mechanism permitting higher absorption in the young is unknown. The immature biliary function at young ages may be involved (Miller et al., 1975; Lonnerdal et al., 1987), thus reducing the capacity of the young to rid itself of an excessive dose of manganese. Neonatal mice did not excrete manganese for the first 17 to 18 days of life, although they absorbed manganese and accumulated it in body tissues, including the brain (Miller et al., 1975).

Biodistribution of Manganese

Manganese can be absorbed and produce toxicity by all routes of administration including dietary. In animals, toxicity of ingested manganese generally appears only after the dietary concentration exceeds 1,000 micrograms/gram of diet (Hurley and Keen, 1987). The NAS/NRC (1989) recommended dietary allowances states that an occasional intake of 10 milligrams of manganese per day by adults can be considered safe.

The NAS/NRC notes that for the young of certain animal species, the homeostatic mechanism for manganese is relatively under-developed (Cotzias et al., 1976). Dose-related increases in whole-brain manganese of up to 10-fold between the first and 15th

day-of-life have been found (Cotzias et al., 1968). Brain manganese rose rapidly prior to the onset of the excretory pathway, mainly via bile (described above in the section on manganese absorption). This early inability to control the manganese concentration in the brain raises concerns for future toxic effects of manganese on the central nervous system that are described above.

Manganese is absorbed and concentrates rapidly in the liver, where its concentration is regulated by excretion into the bile (Rehnberg et al., 1981). Young rats accumulated manganese in the central nervous system, including the cerebrum, hypothalamus, and pituitary at rates much higher than seen in adult animals (Rehnberg et al., 1981). Further, the residence time of manganese in the central nervous system was prolonged in the young animals. The specific form of manganese produced by combustion of MMT, manganese tetroxide, has been found to be absorbed and retained to a greater extent in young rats (Rehnberg et al., 1980).

Manganese absorption appears to be closely associated with pathways for iron absorption (Gruden, 1987; Mena et al., 1980; Lonnerdal, 1987; Sandstrom et al., 1986). Iron absorption is under physiological control. During iron deficiency, the absorption of iron increases. Manganese absorption by iron-deficient subjects has been reported to be more than two-times higher than in iron-replete subjects (Mena et al., 1980).

The parallel absorption of manganese and iron may persist in the disease state. Iron absorption can be abnormally high in patients with idiopathic hemochromatosis; an inherited disorder of iron metabolism associated with progressive and frequently lethal accumulation of body iron. The defect is in the control of iron absorption at the gastrointestinal mucosa, specifically in the concentration of iron-binding proteins (isoferritins) present in the intestinal mucosa. Elevated levels of these proteins permit continued absorption of iron although the subject already has an overload of iron (Whittaker et al., 1989).

Biomarkers

A suitable biomarker for manganese has not been identified, although whole blood manganese concentrations have been used (Keen et al., 1983). Hair manganese will reflect external environmental contamination, as well as internal dose of manganese.

Individual Susceptibility

Data indicate there is marked variation in the fractional absorption of manganese. Manganese shares gastrointestinal

transport carrier-proteins with iron. This variation in iron and manganese absorption appears to be under genetic control. For example, the genetic disease idiopathic hemochromatosis described above. The incidence of idiopathic hemochromatosis in the United States population is about 3 per 1,000 (Cartwright et al., 1979). The incidence of the gene for idiopathic hemochromatosis is approximately twice as high (5 or 6 per 1,000 people) as the occurrence of the clinical disease. Because manganese absorption appears to parallel iron absorption, elevated levels of these proteins may also permit elevated manganese absorption.

There are examples of nongenetic disease that can promote the development of manganese toxicity if they occur concurrent with exposure to relatively high quantities of manganese. An example is biliary dysfunction. The biliary pathway for manganese excretion is critical to controlled excretion of manganese. Any condition that interrupts or reduces excretion of bile abolishes or diminishes the capacity of the body to rid itself of absorbed manganese.

Physiological states also alter manganese absorption, e.g., pregnancy. Kirchgessner et al., (1982) reported that rats in the third portion of pregnancy, absorbed three-times more manganese than did nonpregnant, nonlactating controls.

Dietary Intake and Nutritional Requirements for Manganese

Manganese is a required nutrient for all species studied. Human dietary deficiency has not been identified except for one individual who experienced long-term consumption of a synthetic diet from which manganese was omitted (NAS/NRC, 1989). Signs and symptoms of deficiency include poor reproductive performance, growth retardation, congenital malformations in the offspring, impaired glucose tolerance and abnormal formation of bone and cartilage (NAS/NRC, 1989). There are two known manganese metallo-enzymes: pyruvate carboxylase and superoxide dismutase. Both of these are mitochondrial enzymes. Other enzymes including decarboxylases, hydrolases, kinases, and transferases, are nonspecifically activated by manganese in vitro.

On the average the diet in the United States contains about 1 to 3 milligrams of manganese (NAS/NRC, 1989). The recommended intake of manganese for adults is 2 to 5 milligrams per day. For infants aged birth through 0.5 years, the recommended intake is 0.6 milligrams/day with the recommendation increasing to 0.5 to 1.0 milligrams/day between 0.5 and 1.0 years.

There is wide variation in dietary intake of manganese. Diets appear to contain above 5 milligrams of manganese/day without serious adverse effects identified in the population consuming these diets. However, careful evaluation of individuals with dietary intakes at the upper range of world-wide manganese intake by human populations has not been completed.

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Appendix I

IV-D-78

DRAFT REPORT

SUPPORT FOR CHEMICAL NOMINATION AND SELECTION PROCESS OF THE NATIONAL TOXICOLOGY PROGRAM

NIEHS CONTRACT No. NO1-ES-5-5097

EXECUTIVE SUMMARY OF DATA

METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL

October 31, 1986

Submitted to:

National Toxicology Program
National Institutes of Health
Building 31, Room 2B-55
Bethesda, Maryland 20205

Submitted by:

Dynamac Corporation
The Dynamac Building
11140 Rockville Pike
Rockville, Maryland 20852

Rev. 1/14/87

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NTP EXECUTIVE SUMMARY OF DATA DRAFT

METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL*

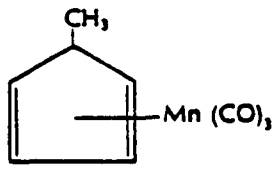
I. Chemical and Physical Information

A. Synonyms: Manganese, tricarbonyl methylcyclopentadienyl
Manganese, tricarbonyl [(1,2,3,4,5-eta)-1-methyl-2,4-cyclopentadien-1-yl]-
2-Methylcyclopentadienyl manganese tricarbonyl
MMT

B. CAS No: 12108-13-3

C. Molecular Formula: $C_9H_7MnO_3$

D. Structural Formula:



E. Molecular Weight: 218.10

F. Physical Properties:

1. Physical State: Dark orange liquid (Verschueren, 1983)
2. Melting Point: 1.5°C (Kirk-Othmer, 1981); 2.22°C (ACGIH, 1980)
3. Boiling Point: 232.8°C (Verschueren, 1983)
4. Flash Point: 110°C, closed cup (ACGIH, 1980)
5. Vapor Pressure: 0.047 mm Hg at 20°C (Verschueren, 1983)
6. Specific Gravity: 1.39 at 20°C (ACGIH, 1980)
7. Refractive Index: No information was found.
8. Solubility in Water: 70 ppm at 25°C (Verschueren, 1983)
9. Solubility in Organic Solvents: Completely soluble in hydrocarbons (Verschueren, 1983)
10. Log Octanol/Water Partition Coefficient: 3.5 estimated (USEPA, 1983)
11. Other: Faintly pleasant odor, decomposes when exposed to light (ACGIH, 1980); half-life of a few seconds in air (Verschueren, 1983)

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*The Environmental Protection Agency has nominated methycyclopentadienyl manganese tricarbonyl for three generation reproductive toxicity studies.

October 31, 1986.

II. Production/Use/Exposure/Environmental/Regulatory Data

A. Production

1. Manufacturing Process

Methylcyclopentadienyl manganese tricarbonyl (MMT) is manufactured by the gradual addition of methylcyclopentadienyl dimer to an agitated mixture of molten sodium metal and diethylene glycol dimethyl ether at 185-190°C. Anhydrous flaked manganese chloride is then added, under agitation at 165°C, to the methylcyclopentadienylsodium formed in the first step, producing bis(methylcyclopentadienyl manganese). The latter product is treated with carbon monoxide at 625 or 650 psi and 193°C to form MMT, which is isolated from the reaction mixture by vacuum distillation (Kirk-Othmer, 1981).

2. Volume

Production volume data for MMT in 1977 were not reported in the public portion of the Toxic Substances Control Act (TSCA) Chemical Substance Inventory (TSCA Inventory) (USEPA, 1985).

The U.S. International Trade Commission (USITC, 1981-1985) did not provide production volume data for MMT from 1980 to 1984 because only one manufacturer reported production of the compound in each of those years (see Section II.A.3). The USITC lists production volume data on a compound only if three or more companies manufacture the compound in a given year.

Ethyl Corporation (1983) reported production of about 4 million pounds of MMT in 1983. Exports of the compound to Canada have apparently accounted for about half of the reported domestic production in recent years (see Section II.B).

CEH (1982) reported that the compound is not produced or consumed in Western Europe or Japan. These data indicate that MMT is not imported into the United States. According to SRI International, the Ethyl Corporation manufacturing plant (see Section II.A.3) has an annual production capacity of about 10 million pounds (CEH, 1982).

3. Producers and Importers

Producers (SRI International, 1985; USITC, 1981-1985; USEPA, 1985)

Ethyl Corporation, Chemical Group
Orangeburg, SC

Ethyl Corporation (1983) reported that it is the sole domestic manufacturer of MMT; the company produces the compound only at the facility listed above.

Importers

No information was found.

4. Technical Product Composition

Ethyl Corporation markets MMT as a product of greater than 97% purity, containing a minimum of 24.4% manganese (Mn) by weight (Ethyl Corporation, 1983).

B. Use

MMT is currently used in domestic applications as an antiknock additive in leaded regular gasoline and as a combustion improver in turbine fuel (Ethyl Corporation, 1983). Ethyl sells approximately 2 million pounds of MMT annually as an antiknock additive

for use at an average concentration of 0.03 to 0.05 g Mn/U.S. gallon of leaded regular gasoline. Sales of the compound as a combustion improver total about 100,000 pounds annually, worldwide. Use of the compound in this application is decreasing due to the greater efficiency of modern turbine engines.

MMT is also currently used as an antiknock additive in essentially all of the unleaded gasoline marketed in Canada (Ethyl Corporation, 1983). The compound is added to unleaded premium gasoline at a concentration of about 0.06 g Mn/U.S. gallon and to unleaded regular at about 0.04 g Mn/U.S. gallon. A maximum concentration of 0.068 g Mn/U.S gallon is allowed under Canadian law.

Prior to a ban on the use of MMT as an additive to domestic unleaded gasoline by the EPA, effective September 1978, 60% of domestic refining capacity used MMT in unleaded gasoline in 1977 (Ethyl Corporation, 1983; CEH, 1982). The EPA banned the compound from domestic unleaded fuels based on evidence that the use of MMT results in a slight increase in hydrocarbon emissions at the tail pipe (Ethyl Corporation, 1986).

C. Occupational Exposure

The National Occupational Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1972 to 1974, estimated that 22,967 workers in 720 plants were potentially exposed to MMT in the workplace (NIOSH, 1976). These estimates were derived from observations of the actual use of MMT (less than 1% of total estimate) and the use of generic products suspected of containing the compound (greater than 99% of total estimate). The largest number of exposed workers was in the machinery (except electrical) industry (refer to Enclosure 1).

The occupational groups with the largest number of exposed workers were drill press operators, tool and die makers, lathe and milling machine operators, machinists, packers and wrappers (except meat and produce), and machine operators (not specified) (refer to Enclosure 2).

NIOSH conducted a second workplace survey, the National Occupational Exposure Survey (NOES), from 1980 to 1983 (NIOSH, 1984). Preliminary data from NOES indicated that 1,082 workers in 10 plants were potentially exposed to the compound in the workplace in 1980. All of these workers were employed in the petroleum and coal products industry; most of them were janitors and cleaners and industrial truck and tractor equipment operators (refer to Enclosure 3). Unlike NOHS, the NOES estimates were based only on observations in which the surveyor observed the actual use of the compound.

Ethyl Corporation (1986) reported that MMT is currently used only at refineries. Occupational exposure to MMT is virtually absent during blending and manufacturing processes, which are closed-system operations. The only documented exposures to MMT have resulted from accidental sprays or spills of MMT during material transfer operations. Approximately 70 workers are potentially exposed to MMT in manufacturing, handling, or maintenance at Ethyl's MMT plant. Refinery and transport workers are also potentially exposed to MMT.

The NIOSH Tradename Ingredient Data Base of NOHS listed MMT as a constituent of one product used in industrial applications (refer to Enclosure 4) (NIOSH, 1976). The concentration of MMT in the product was 96%.

The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted an 8-hour time-weighted average threshold limit value of 0.2 mg Mn/m^3 and a short-term exposure limit

(STEL) threshold limit value of 0.6 mg Mn/m^3 for MMT (ACGIH, 1985). A "skin" notation was designated, indicating the potential for dermal absorption of toxic amounts of the compound. ACGIH further recommended that appropriate measures be taken to prevent dermal contact and cutaneous absorption. The ACGIH (1984) proposed that the adopted STEL for MMT be deleted on the basis that the information available relates to chronic effects. The deletion of this value is recommended until acute toxicological data and industrial hygiene experience become available to provide a basis for quantifying what the STEL should be.

Ethyl Corporation (1983) stated that the results of periodic monitoring of operators at their manufacturing plant indicate that most concentrations of MMT in workplace air have been less than 40 µg Mn/m^3, the detection limit of their personal monitoring method. Exposures as high as 100 µg Mn/m^3 have been detected in a few instances.

D. Consumer Exposure

Exposures to MMT may occur through its use as an antiknock additive in leaded regular gasoline. Low-level inhalation or dermal exposure may occur during self-service pumping of the gasoline.

E. Environmental Data

Coe et al. (1980, as cited in USEPA, 1983) were unable to detect MMT (detection limit 0.05 ng MMT/m^3) in air in Toronto, Canada, where MMT is used extensively in unleaded gasoline. The only location in which MMT was found in air was an underground parking garage where levels of 0.1 to 0.3 ng/m^3 were detected.

MMT in gasoline is photolytically unstable, decomposing in the presence of both light and oxygen (Ter Haar et al., 1975). Almost all of the manganese is converted to a mixture of solid

manganese oxides and carbonates. The organic portion of the solid decomposition products appears to be a complex mixture of acids, esters, and hydrocarbon polymers. A half-life of 8-18 seconds was calculated for MMT by Ter Haar et al. (1975). Although they were unable to experimentally determine a definite half-life, the authors concluded that the survival of MMT in the atmosphere would be either seconds or minutes at the longest. The log octanol/water partition coefficient of MMT has been estimated to be 3.5, suggesting the potential for bioconcentration.

F. Regulatory Status

The Occupational Safety and Health Administration has not established a permissible exposure limit for MMT (OSHA, 1983).

MMT has not been scored or studied by the TSCA Interagency Testing Committee (ITS, 1985).

MMT is regulated as an automobile fuel additive under Section 211f of the Clean Air Act (USEPA, 1981). This regulation prohibits the commercial use of certain automotive fuels and fuel additives. Ethyl Corporation applied for a waiver of this prohibition to permit the use of MMT at a concentration of up to 1/64 g of Mn per gallon of unleaded gasoline; however, this waiver was denied. The use of MMT in unleaded gasoline has not been approved because of concern that its use results in a slight increase in hydrocarbon emissions at the tail pipe (Ethyl Corporation, 1986).

No other Federal regulations relating to MMT were found.

III. Toxicological Effects

A. Human Data

1. Acute: No cases of overexposure resulting in lethality in

humans were found. Ethyl Corporation (1977) reported that MMT liquid produces a slight burning sensation on the skin and MMT vapors produce a metallic taste when inhaled. In unsubstantiated reports, six men with skin exposure for up to 30 minutes, showed signs and symptoms that included headache, nausea, gastrointestinal discomfort, dyspnea, chest tightness, and paresthesia. All signs and symptoms appeared 5 minutes to 1 hour after exposure and completely subsided in 2 hours in four cases. Two workers reported a vague abdominal distress that persisted for 2 days. A well-documented incident involved the case of four employees at a refinery who were exposed to MMT vapors for approximately 5 minutes while pouring 25 gallons of MMT into a large steam-heated pot. No symptoms were reported in any of the four workers. Manganese concentrations in the exposed workers' urine taken 3 hours after the incident were 23, 87, 20, and 10 µg/L. Twenty-three hours after exposure, urine samples contained 8, 22, 5, and 10 µg Mn/L, respectively. The workers were symptom free, and no adverse effects have since been reported.

In another exposure incident, the clothes of two men were wetted by MMT during the pumping of MMT out of a drum. Although their hands and face were protected by rubber gloves and air masks, the remainder of their bodies were moistened by the liquid for approximately 1.5 hours. The men complained of a slight burning sensation on their skin. In both men, hematology parameters, blood pressure, and pulse were normal and muscular coordination was good. Urine Mn levels measured on the day of exposure were 137 and 46 µg/L. A few weeks following exposure, urine Mn levels were within the normal range, and no adverse effects had developed.

Overexposure to MMT may affect the central nervous system and lead to convulsions, respiratory depression, cyanosis, and coma. Additional adverse effects following overexposure

can include labored breathing, lethargy, lacrimation, eye inflammation, and nasal discharge (Ethyl Corporation, 1976).

MMT is not irritating to the skin on single contact and is not known to cause cutaneous sensitization. However, it does appear to penetrate the skin very rapidly; 5-15 mL of MMT spilled on the hand and wrist of a worker was claimed to have caused the symptoms of "thick tongue," giddiness, nausea, and headache within 3-5 minutes (ACGIH, 1980).

2. Epidemiological Evidence/Case Reports: No information was found in the information sources searched.

3. Chemical Disposition: No information was found.

4. Biochemical Effects: No information was found.

5. Carcinogenicity/Chronic: No information was found.

6. Teratogenicity and Reproductive Effects: No information was found.

B. Animal Data

1. Acute: The acute systemic toxicity data for MMT in various laboratory animals are presented in Table 1.

Pfitzer et al. (as cited in NAS, 1973) investigated the acute toxicity of MMT in five laboratory species by the oral route and two species by the dermal route. The LD_{50} values are included in Table 1. In general, MMT toxicity was dependent on the species (with rats the most susceptible, followed by rabbits, mice, dogs, and guinea pigs). Additionally, females were more sensitive than males, and oral toxicity was considerably greater than skin toxicity. Toxic responses appeared promptly after exposure regardless of species or route and included mild excitement and hyperactivity, tremors,

severe tonic spasms, weakness, slow and labored respiration, occasional mild clonic convulsions, and terminal coma. Animals surviving convulsive episodes failed to thrive, lost weight rapidly, and died after a few days. Primary pathological effects occurred in the kidneys, liver, and lungs.

Hakkinen and Haschek (1982) also compared species differences in acute toxicity. MMT was administered by intraperitoneal injection into mice, rats, and hamsters. The LD_{50} values are presented in Table 1. The most sensitive species was the rat, followed by the mouse and hamster. Death, preceded by dyspnea, generally occurred in the first 72 hours following treatment. Salivation, eye irritation, rough hair coat, and weakness were also noted. At necropsy, lung wet weight was increased, and mottling and/or pallor of the liver were frequently observed.

The authors also studied the pulmonary toxicity of MMT in these three species by histopathological and biochemical analyses. Mice, rats, and hamsters received a single intraperitoneal injection of purified MMT in corn oil at doses of 120, 5.0, and 180.0 mg/kg, respectively. Control animals received corn oil.

Pulmonary effects, in particular, interstitial pneumonitis, Clara cell necrosis, and bronchiolar damage, were observed in all species by 1-2 days. In addition to the pulmonary changes, histopathologic changes were present in the kidneys (all species), liver (mouse and hamster), and adrenals (mouse) 1 and 2 days after MMT treatment. MMT treatment significantly ($p < 0.05$) increased <u>in vivo</u> incorporation of thymidine into lung DNA within 1-2 days in all three species. Peak incorporation occurred on day 4 for the mice and on day 2 for the hamsters and rats. These results suggest that the mouse, rat, and hamster have different susceptibilities to MMT-induced lung injury.

Table 1. Acute Toxicity of MMT in Laboratory Animals

Species	Strain	Route	No./Sex	Dose	Effects	Reference
Mouse	CD-1	Orl	48/F	28-320 mg/kg (10% w/v solution)	LD_{50}: 230 mg/kg (95% confidence limit 167-293 mg/kg)	Hinderer (1979)
			12/F	450, 635 mg/kg (20% w/v solution)	Urinary staining; pilo-erection; mottling and discoloration of the liver; intestines were fluid filled and spotted.	
Mouse	—[a]	Orl	-/-	—	Approximate LD_{50}: 350 mg/kg	Pfitzer et al. (as cited in NAS, 1973)
Mouse	—	Orl	64/-	105-593 mg/kg	LD_{50}: 251.9 mg/kg (95% confidence limit 232.6-280.5 mg/kg)	Ohnishi (1978)
Mouse	CFI	Orl	61/M	1.0-500 mg/kg	LD_{50}: 34 mg/kg	Majima (1985)
			48/F		LD_{50}: 60 mg/kg	
Mouse	—	Ihl	-/-	300-400 mg/m^3/1 hr 500-700 mg/m^3/1 hr 1000 mg/m^3/1 hr	Some mortality 50% mortality 100% mortality	Ohnishi (1978)
			64/-	32.0-111 mg/m^3/4 hr	LC_{50}: 58.6 mg/m^3	
		Ip	64/-	105-593 mg/kg	LD_{50}: 151.5 mg/kg (95% confidence limit 139.5-164.7 mg/kg)	
Mouse	BALB/C	Ip	16/F	100-174 mg/kg	LD_{50}: 138 mg/kg (95% confidence limit 120-159 mg/kg)	Hakkinen and Haschek (1982)
Rat	COBS	Orl	80/-	15-150 mg/kg	LD_{50}: 58 mg/kg Dose related histopatho-logical changes were found in the lung, liver, and kidneys of surviving animals	Hysell et al. (1974)
Rat	Sprague-Dawley	Orl	40/M-F	10% w/v solution	LD_{50}: 58 mg/kg (95% confidence limit 37.4-89.9 mg/kg) Salivation, weakness,	Hinderer (1979)

Table 1. Acute Toxicity of MMT in Laboratory Animals (continued)

Species	Strain	Route	No./Sex	Dose	Effects	Reference
					and diarrhea; lungs were dark red and the intestinal tract and viscera were discolored. Females were more sensitive than males.	
Rat	Sprague-Dawley	Orl	20/M	30.0–118.0 mg/kg	LD_{50}: 50 mg/kg (95% confidence limit 38–67 mg/kg)	Hanzlik et al. (1980b)
Rat	—	Orl	-/-	—	Approximate LD_{50}: 9.0–176 mg/kg	Pfitzer et al. (cited in NAS, 19
Rat	Sprague-Dawley	Inh	90/M	-/1 hr	LC_{50}: 247 mg/m^3 (95% confidence limit 229–271 mg/m^3) Decreased activity, slight conjunctivitis, dyspnea, and lung hemorrhage.	Hinderer (1979)
				-/4 hr	LC_{50}: 76 mg/m^3 (95% confidence limit 67–87 mg/m^3) Decreased activity, dyspnea, eye irritation, weight loss, and minimal occurrence of hemorrhagic foci in the lungs.	
Rat	—	Skn	-/-	10% solution in peanut oil/6 hrs	Toxic at 665 mg/kg	Pfitzer et al. (cited in NAS, 19
Rat	Sprague-Dawley	Ipr	16/M	9.5–76 mg/kg	LD_{50}: 23 mg/kg (95% confidence limit 13–38 mg/kg)	Hanzlik et al. (1980b)
Rat	Albino	Ipr	16/F	2.5–20 mg/kg	LD_{50}: 6 mg/kg (95% confidence limit 4–8 mg/kg)	Hakkinen and Haschek (1982)
Hamster	LV_6/LAK	Ipr	16/F	120–405 mg/kg	LD_{50}: 270 mg/kg (95% confidence limit 213–341 mg/kg)	Hakkinen and Haschek (1982)
Guinea pig	—	Orl	-/-	—	Approximate LD_{50}: 900 mg/kg	Pfitzer et al. (cited in NAS, 19

Table 1. Acute Toxicity of MMT in Laboratory Animals (continued)

Species	Strain	Route	No./Sex	Dose	Effects	Reference
Rabbit	—	Orl	-/-	—	Approximate LD_{50}: 95 mg/kg	Pfitzer et al. (as cited in NAS, 1973)
Rabbit	—	Skn	-/M	Undiluted	Approximate LD_{50}: 1700 mg/kg (24 hr)	Pfitzer et al. (as cited in NAS, 1973)
Rabbit	—	Skn	-/-	Neat	LD_{50}: 140 mg/kg[b] (95% confidence limit 122-159 mg/kg) LD_{50}: 196.7 mg/kg[b] (95% confidence limit 151.9-254.7 mg/kg) LD_{50}: 420 mg/kg[b] (95% confidence limit 170-670 mg/kg) LD_{50}: 795 mg/kg[b] (95% confidence limit 568-1113 mg/kg) Toxicity varied from polyapnea to vocalization, excitation, ataxia, tremors, cyanosis, and convulsions. Body weight loss, erythema, and edema were noted. Gross pathology revealed bloody diarrhea; lung abnormalities; discoloration of the liver, kidneys, and spleen; congested kidneys; and swollen livers, kidneys, and spleens.	Hinderer (1979)
Dog	—	Orl	-/-	—	Approximate LD_{50}: >600 mg/kg	Pfitzer et al. (as cited in NAS, 1973)

[a]Data not provided.
[b]Dermal LD_{50} studies were performed at different laboratories and summarized by Hinderer (1979).

Hanzlik et al. (1980b) studied the toxicity of MMT in rats following oral and intraperitoneal administration. The LD_{50} values are presented in Table 1. Microscopic examinations of animals that died within 24 hours revealed that their lungs were grossly distended with a blood-containing fluid. Injury to the liver and kidneys was very minor when compared to the lungs.

The authors also investigated the toxicity of MMT in rats following phenobarbital (PB) pretreatment of 60 mg/kg given intraperitoneally for 3 days. A statistically significant ($p < 0.02$) difference in survival was observed, with 10/10 pretreated rats surviving compared to 1/10 nonpretreated rats following a single oral dose of 125 mg/kg MMT (2.5 times the LD_{50} dose for this route). PB pretreatment was also found to shift the site of tissue injury from the lungs to the liver. Liver injury was evidenced in pretreated animals by a significant increase ($p < 0.05$) in plasma glutamic pyruvic transaminase levels, and a significant decrease ($p < 0.05$) in the glucose-6-phosphatase content of the liver. In addition, following an intraperitoneal injection of ^{3}H-MMT (30 mg/kg), the Mn concentration in the bile of pretreated animals was approximately 50- to 300-fold higher than that of bile from non-treated rats. Following an intravenous injection of ^{3}H-MMT (10 mg/kg) to PB-pretreated and control rats, the cumulative biliary excretion of MMT metabolites was significantly greater ($p < 0.05$) for the pretreated group when compared to the control group.

Haschek et al. (1982) studied the pulmonary toxicity induced by MMT in mice and rats. Female BALB/C mice and male Fischer rats (number not specified) received a single intraperitoneal injection of MMT in corn oil at a dose of 120 and 8.4 mg/kg, respectively. Control animals received corn oil only. MMT produced selective necrosis of non-ciliated bronchiolar epithelial cells (Clara cells) in both species; however, Clara cell necrosis was more severe in the mouse than in the rat.

In another experiment, pretreatment of mice with piperonyl butoxide (1600 mg/kg, administered intraperitoneally), an inhibitor of the mixed-function oxidase system, enhanced pulmonary toxicity and mortality following a single interperitoneal injection of 90 mg/kg MMT.

Witschi et al. (1981a) studied the effect of oxygen (O_2) exposure on MMT-induced lung damage. Seventeen female BALB/C mice were given a single intraperitoneal injection of 120 mg/kg of MMT in corn oil. A control group consisting of 17 animals received corn oil only. Nine treated and nine control animals were exposed to 70% O_2 for 6 days and then returned to room air. The extent of fibrotic changes in the lungs was quantitated by measuring total lung hydroxyproline 3 weeks after the injections. Total lung collagen was significantly increased ($p < 0.05$) only in mice exposed to MMT + O_2.

In a later study, Hakkinen et al. (1983) provided evidence for a species difference in response to MMT-induced lung toxicity following exposure to O_2. Female BALB/C mice and CD/CR rats received a single intraperitoneal injection of MMT in corn oil at 120 and 5 mg/kg, respectively. Control groups received corn oil by the same route. Immediately after each treatment, half of the MMT treated animals and half of the controls were exposed for 6 days to 80% O_2 and then returned to normal room air. Animals were sacrificed 3 weeks after the initial treatment of MMT.

In the mice, MMT alone caused a nonsignificant increase in total lung hydroxyproline content. The combined treatment of MMT + O_2 produced interstitial fibrosis and a statistically significant ($p < 0.05$) increase in lung hydroxyproline when compared to both the corn oil controls or animals treated with MMT alone.

In the rats, MMT alone produced a significant increase ($p < 0.05$) in total lung hydroxyproline content. Oxygen exposure failed to further increase lung collagen content. Histologic examination revealed that lungs of rats exposed to MMT + O_2 were indistinguishable from rats treated with MMT alone.

Two reports have described irritation studies of MMT. In one, Campbell et al. (1975) scored MMT as a nonirritant following a dermal irritation study using six male albino rabbits. MMT (0.1 mL neat) was applied to both abraded and intact skin. In the other, Hinderer (1979) tested MMT for dermal and ocular irritation in groups of six rabbits (strain and sex not specified). MMT (dose not specified) was found to be a moderate skin irritant, inducing erythema and slight edema in both abraded and intact skin. The author reported that MMT did not induce eye irritation; however, no details were provided.

2. Chemical Disposition: No specific studies were found that measured the degree of absorption of MMT.

Ohnishi (1978) exposed mice (strain, sex, and number not specified) to MMT mist and vapor at concentrations of 100-1000 mg/m^3 for 1 hour or at 32-111 mg/m^3 for 4 hours. After 1 hour of exposure, organic Mn was higher in the liver and kidneys than in the lungs and brain. After the 4-hour exposure, inorganic and organic Mn was detected in a dose-dependent manner in the livers, lungs, and kidneys.

The author also exposed six mice to MMT at concentrations of 0.1-0.3 and 1-2 mg/m^3, 22 hours/day for 21 days, and three rats to 0.1-0.3, 1-2, and 5-7 mg/m^3, 22 hours/day for 4

days. In the mice, Mn content was dose-dependent in the kidneys, liver, lungs, spleen, and blood. In the rats exposed for 4 days, Mn was measured in all the organs, but the concentrations varied.

Majima (1985) measured the Mn concentration in the livers and kidneys of male and female CF-1 and C57BL/6 mice (number not specified) following a single oral dose of 10 mg/kg MMT. The highest Mn concentrations were measured in the livers and kidneys of male CF-1 mice on days 1 and 2. Mn concentrations had returned to control values in the males and females of both species 3-4 days postdosing.

Hysell et al. (1974) determined the concentrations of Mn in rat tissues following a single oral dose of MMT. Seventy COBS rats received MMT in Wesson oil at doses ranging from 15 to 150 mg/kg. A control group of 10 rats received only Wesson oil. The Mn concentration in tissues from animals dying after exposure to MMT was dose dependent. The highest concentrations were found in the duodenum, followed by the kidney, liver, lung, brain, and heart. By 14 days post-exposure, the Mn concentration in most tissues of exposed animals were similar to the controls. However, Mn content in the lung was approximately 6- to 12-fold higher in the exposed animals.

Hanzlik et al. (1979) conducted a series of <u>in vitro</u> experiments designed to determine if the cytochrome P-450 system was important in the biotransformation of MMT. Rat liver microsomes were prepared from PB-pretreated (60 mg/kg given intraperitoneally for 3 days) rats and control (non-pretreated) rats and incubated with 0.5 mM MMT under various conditions. The rate of MMT metabolism in the presence of PB-induced microsomes was approximately twice

that of the controls. MMT metabolism was shown to require molecular oxygen and the NADPH-generating system, and it was inhibited by both carbon monoxide and the cytochrome P-450 inhibitor N-decylimidazole.

Hanzlik et al. (1980a) studied the metabolites of MMT formed in rats pretreated with phenobarbital (PB). They found that oral administration of tritiated ^{3}(H) MMT (125 mg/kg) to rats that had been given daily doses of sodium phenobarbital (60 mg/kg) for 3 days resulted in excretion of 81% of the total radioactivity in urine, and 2 to 4% in feces within 48 hours. The two major metabolites identified in the urine, $(CO)_3MnC_5H_4COOH$ and $(CO)_3MnC_5H_4CH_2OH$, amounted to 67% and 14% of the total urinary tritium, respectively. These metabolites were excreted in substantial quantities in bile but underwent reabsorption and excretion by the kidney. The authors also studied the biliary excretion of MMT metabolites following intravenous administration of ^{3}H-MMT (10 mg/kg) in control and PB pretreated rats. The results indicated that PB pretreatment doubled the rate of biliary excretion of MMT metabolites. In another experiment the authors studied <u>in vitro</u> kinetics of MMT metabolism by lung and liver microsomes prepared from control and PB treated rats. MMT was rapidly metabolized by a cytochrome P-450 dependent process inducible in liver but not in lung microsomes.

Moore et al. (1974) studied whole-body retention, excretion, and tissue distribution of ^{54}Mn following oral and intravenous dosing of ^{54}Mn-labeled MMT in male Charles River rats. An initial rapid excretion of most of the ^{54}Mn occurred following both routes of exposure. Analysis of the urine and feces after dosing indicated that MMT was rapidly metabolized, and that the ^{54}Mn was excreted in the inorganic form. The liver, kidneys, and lungs contained the highest concentrations of ^{54}Mn. High levels of ^{54}Mn were also found in the urine. Results of <u>in vitro</u> biotrans-

formation assays revealed that the liver showed the highest activity for MMT metabolism. MMT was also metabolized in the lungs, kidneys, and, to a small extent, in the brain.

3. Biochemical Effects: Autissier et al. (1977, as cited in USEPA, 1983) studied the effects of MMT on oxidative phosphorylation in rat liver mitochondria. MMT inhibited both electron and energy transfer. The manganese tricarbonyl moiety appeared to be responsible for these effects.

Gianutsos and Murray (1982) examined the changes in the concentrations of dopamine (DA), gamma-aminobutyric acid (GABA), and choline acetyltransferase (CAT) in the brains of male CD-1 mice following long-term administration of MMT. Mice received subcutaneous injections of MMT, diluted in propylene glycol, at doses of 10, 20, or 80 mg/kg on alternate days for up to 3 weeks. Control mice received subcutaneous injections of propylene glycol on the same schedule. Twenty-four hours later the animals were sacrificed, and levels of DA, GABA, and CAT were measured in various areas of the brain. DA was significantly ($p < 0.05$) reduced in both the olfactory tubercle and striatum in the 80 mg/kg group and in the striatum in the 20 mg/kg group. Brain Mn concentrations were twofold higher in the 80 mg/kg group than in the control group (1.44 vs. 0.60 µg/g wet weight). GABA levels were significantly ($p < 0.05$) elevated at 80 mg/kg in the striatum and substantia nigra, but not in the cerebellum. The activity of CAT was unchanged in all the brain regions examined.

In order to determine if the effects of MMT on brain DA and GABA were the result of long-term administration, other groups of mice received single injections of MMT (80 mg/kg) and were sacrificed either 1 or 21 days after injection. There were no significant changes in DA or GABA concentrations in any of the brain regions examined.

4. Prechronic: Pfitzer et al. (as cited in NAS, 1973) exposed mice, rats, guinea pigs, rabbits, cats, and dogs (number, strain, and sex not specified) by inhalation to MMT for 7 hours/day, 5 days/week for up to 30 weeks. Concentrations of 14-17 mg/m^3 of MMT produced mortality in mice and rats but not in the other species. Lower concentrations produced no deaths in any species (no details were provided). Toxic responses appeared promptly after exposure, and included mild excitement and hyperactivity, tremors, severe tonic spasms, weakness, slow and labored respiration, occasional mild clonic convulsions, and terminal coma. Animals surviving convulsive episodes failed to thrive, lost weight rapidly, and died after a few days. Primary pathological changes occurred in the pulmonary system.

Ohnishi (1978) exposed groups of mice and rats (strain, sex, and number of animals not specified) to MMT vapors at concentrations of 5-7 mg/m^3 for 22 hours/day for 28 days or for 6 hours/day for 28 days. Animals in all groups showed a marked decrease in body weight and a high mortality. Rats and mice were also exposed to MMT at concentrations of 1-2 mg/m^3 for 22 hours/day for 28 days. These animals showed a suppressed increase in body weight and slight histological changes in the lung. Exposure of rats and mice to 0.1-0.3 mg/m^3 MMT for 22 hours/day for 28 days resulted in no abnormal findings. No further details were provided in the English abstract of the paper.

Ethyl Corporation (1978b) conducted a 12-week inhalation toxicity study of MMT in Swiss mice, Sprague-Dawley rats, and cynomolgus monkeys. There were three test groups/species, plus an untreated control group/species. Each group was comprised of 10 animals/sex, except the monkeys, where only 6 males/group were used. The animals were exposed to MMT vapors at concentrations of 0.0 µg/L (Group I), 0.3 µg/L (Group II), 3.0 µg/L (Group III), and 30.0

µg/L (Group IV), 6 hours/day, 5 days/week for 12 weeks. Animals were observed daily for mortality and clinical signs of toxicity. Body weights were recorded prior to exposure, twice per week for the first 2 weeks, and weekly thereafter. A standard battery of hematology, serum chemistry, and urinalysis tests were run on one-half of the rats and all of the monkeys at termination (12 weeks). Hematology tests were also conducted at 6 weeks. After 12 weeks of exposure all surviving mice, rats, and one-half (3) of the monkeys in each group were sacrificed, and gross necropsies were performed. The remaining three monkeys were sacrificed 14 days postexposure. At necropsy, the heart, liver, kidneys, spleen, brain, lungs, trachea, and gonads were weighed for organ weight/body weight analyses. A detailed histopathological examination was performed on five male and five female mice and rats from Group I (control) and Group IV (30.0 µg/L), as well as from all monkeys.

In the mouse study, high mortality (20% of the males and 50% of the females) and severe weight loss resulted in the sacrifice of Group IV animals after 5 weeks of exposure. Decreases in body weight were seen in these animals within 2 weeks, along with rough hair coat, lethargy, and dyspnea. The lungs showed varying degrees of hyperplasia, metaplasia, epithelial erosions, and fibrosis. Group III mice showed decreases in body weight later in the study period. In addition, the kidney and liver (female) and kidney (male) weights were elevated in this group. The female mice in Group II showed an increase in the liver and kidney weights and a decrease in the heart weight.

In the rat study, deaths occurred in three females in Group III and in one male and two females in Group IV. Both sexes in Group IV showed loss of body weight within 2 weeks, and exhibited rough hair coat, lethargy, and dyspnea. No hemato-

logic effects were observed at any level. Blood urea nitrogen was elevated, and glucose was depressed in both sexes in all MMT-exposed groups. Serum alkaline phosphatase was elevated in both sexes in Group IV.

Exposure-related histologic alterations were observed in the lungs of rats in the highest exposure group, including an increase in alveolor macrophages, pneumonitis, pleuritis, and alveolar wall thickening.

In the monkey study, no mortality or treatment-related effects in body weight, hematology, organ weight parameters, or calcium and phosphorus levels were seen. With the exception of vacuolation in the white matter of the brain stem and cerebellar folia, no exposure-related microscopic alterations were found in the monkeys. There was minimal vacuolation in three of six monkeys in Group III, but there was moderate vacuolation in five of six monkeys in Group IV.

Results from this study indicate that the mouse is the species most sensitive to MMT vapor exposures, followed by the rat and monkey, respectively. There also appears to be a sex-related difference in response, with female rodents being more sensitive than male rodents.

Pfitzer et al. (as cited in NAS, 1973) conducted studies following repeated dermal applications (species, strain, sex, number of animals, and number of applications not specified) of MMT added to gasoline at concentrations up to 16 mg/mL. No adverse effects were observed that were not attributable to the gasoline itself.

5. Carcinogenicity/Chronic: Witschi et al. (1981b) investigated the lung tumor-promoting potential of MMT in strain A/J mice. Sixty female mice were injected intraperitoneally with 500 mg/kg urethan, and an equal number of mice received

0.9% NaCl. A week later, 30 mice each from the urethan and NaCl treatment groups received 80 mg/kg MMT in corn oil intraperitoneally (for a total of six weekly injections), while the remaining mice from the urethan and NaCl treatment groups received corn oil alone. All animals were sacrificed 4 months following urethan treatment. MMT failed to enhance lung tumor formation in mice treated with urethan. There was 100% incidence in both the urethan + MMT and the urethan + corn oil groups. No increase in multiplicity of tumors resulted (7.6 vs. 8.3 tumors/mouse in urethan + MMT and urethan + corn oil groups, respectively). MMT alone did not increase the incidence of spontaneously occurring lung tumors (11% in 0.9% NaCl + MMT vs. 13% in 0.9% NaCl + corn oil groups).

6. Teratogenicity and Reproductive Effects: The teratogenic potential of MMT was investigated using Charles River COBS CD rats (Ethyl Corporation, 1979). Four treatment groups of 25 rats each and a control group consisting of 125 females were used. MMT was administered in corn oil at dose levels of 2.0, 4.5, 6.5, and 9.0 mg/kg/day orally by gavage on days 6 through 15 of gestation. The control group received corn oil only. Cesarean sections were performed on the surviving females on day 20 of gestation. Females were observed daily for mortality and clinical signs of toxicity. Implantation sites, the number of total implantations and corpora lutea, early and late resorptions, and maternal liver weights were recorded. All fetuses were examined for body weights, crown-rump length, sex, and external and visceral or skeletal malformations and variations.

At the dose level of 9.0 mg/kg/day, a slight increase in matting and staining of the anogenital haircoat was observed. There were no biologically meaningful differences in appearance and behavior in the other dose groups. One maternal death occurred in the 9.0 mg/kg/day group, and was attributed

to pneumonia. There were no treatment-related differences in reproductive parameters, e.g., resorptions, implantations and viable fetuses. A reduction in mean maternal body weight gain over the entire gestation period was noted in the dams from all the test groups when compared to the control group. A slight reduction in mean fetal body weight was observed in all the test groups as compared to the control group. The only malformation observed was an increased incidence of bent ribs at all the MMT dose levels when compared to the control group. Based on the historical control data, bent ribs were considered a common finding in CD rats.

Ethyl Corporation (1978a) conducted a Segment II teratology study with MMT in rats. Pregnant Long-Evans female rats received MMT in corn oil orally by gavage at dose levels of 5, 10, 20, or 40 mg/kg/day on days 6 through 15 of gestation. Control rats received corn oil. The parameters evaluated included maternal weight gain, physical observations, pregnancy, mortality, and reproduction data (implantations, number of fetuses, and resorptions). Fetal parameters included viability indices, fetal weight, size, sex ratios, and ossification variations. Teratology conclusions were based on fetal external, soft tissue, and skeletal abnormalities.

At dose levels of 5 and 10 mg/kg/day, maternal weight gain during the treatment period was significantly lower ($p < 0.01$) when compared to controls. Additionally, the dams suffered from epistaxis, rapid breathing, and urinary incontinence. Reproduction and fetal data were comparable to the control group. A slight increase (not statistically significant) in ocular malformations was observed at the 10 mg/kg dose level. No embryotoxicity was noted.

At the 20 mg/kg dose level, MMT caused high maternal mortality (70%), a significant ($p < 0.01$) reduction in maternal

body weight gain, decreased rate of pregnancy, cachexia, alopecia, and dehydration. Adrenal enlargement was also noted in several females. Only 55 fetuses (5 litters) were recovered for examination. There was a significant ($p < 0.01$) decrease in the percentage of live fetuses and a significant ($p < 0.01$) increase in the percentage of resorbed fetuses. Fetuses had lower body weights and increased incidence of skeletal ossification variants. Thirty-nine percent of the fetuses had either ocular malformations or vertebral defects. At this dose level, MMT demonstrated severe maternal toxicity and embryotoxicity. Mean fetal crown-rump lengths were comparable between the MMT-treated and control groups.

The dose level of 40 mg/kg was highly toxic and led to 100% mortality of the dams within the first 5 days of treatment. No fetuses were recovered for examination. The authors concluded that MMT was not embryotoxic or teratogenic at 5 mg/kg/day but could not assess the teratogenic potential of MMT at either 10 or 20 mg/kg/day.

Majima (1985) administered MMT (10 mg/kg) to six pregnant CF-1 mice on day 12 of gestation. Twenty pregnant females served as controls. MMT had no adverse effects on the number of corpora lutea, implantations, and living fetuses. The concentration of MMT was significantly (p value not given) higher in the livers of the treated dams as compared to the untreated controls, with slight increases (not significant) in the lungs and pancreas.

C. Genotoxicity

SRI (1977, as cited in USEPA, 1983) evaluated the mutagenic potential of MMT in microbial (Salmonella/microsome and Saccharomyces cerevisae) assays both with and without metabolic activation. The S. typhimurium strains employed were TA98, TA100, TA1535, TA1537, and TA1538. MMT was nonmutagenic in all assays.

Bio/dynamics (1977, as cited in USEPA, 1983) tested MMT for mutagenicity in a dominant lethal assay in mice. The compound was administered by gastric intubation to male mice at dose levels of 80 and 160 mg/kg/day for 5 consecutive days. No dominant lethal effects were observed.

D. Structure-Activity Relationships

No compounds that are structurally related to MMT have been selected for toxicological testing by the National Toxicology Program (NTP) (CHEMTRACK, 1986).

IV. Nomination Source

A. Source: Environmental Protection Agency (USEPA, 1984)
B. Recommendation: Three-generation reproductive toxicity studies
C. Rationale/Remarks: Moderate production volume, high skin absorption, and toxic effects have been observed in humans.
D. Priority: None given
E. Date of Nomination: July 1984

V. Chemical Evaluation Committee Review

A. Date of Review: April 29, 1986
B. Recommendations: No testing
C. Priority:
D. NTP Chemical Selection Principle(s):
E. Rationale/Remarks: -Low potential for consumer exposure. Not used in U.S. as a gasoline additive.

VI. Board of Scientific Counselors Review

A. Date of Review: November 25, 1986
B. Recommendations: No testing
C. Priority: —
D. Rationale/Remarks: -Low exposure
-Reconsider if new uses developed for MMT

VII. Executive Committee Review

A. Date of Review:

B. Decision:

VIII. Information Sources

This report was prepared by a multidisciplinary team of scientists and technicians. Dr. John Bruno was the principal author.

The information resources used in preparing this review include the automated data bases listed below, journal articles, general reference materials, and contractor/agency reports.

ON-LINE DATA BASES SEARCHED

MEDLARS

CHEMLINE	
RTECS	
TDB	
MEDLINE	1983-Present
TOXLINE	1966-Present
TOX 76	1976-1980
TOX 65	1940-1975
CANCERLIT	1963-Present
CANCERPROJ	1978-1981

DIALOG

AGRICOLA	1970-Present
AQUALINE	1960-Present
BIOSIS PREVIEWS	1969-Present
CA SEARCH	1967-Present
CHEMICAL EXPOSURE	1974-Present
CIN (Chemical Indust. Notes)	1974-Present
CLAIMS/U.S. PATENT ABSTRACTS	1950-Present
CONFERENCE PAPERS INDEX	1973-Present
CRGS (Chemical Regulations and Guidelines) System)	1982-Present
EMBASE	1974-Present
ENVIROLINE	1971-Present
ENVIRONMENTAL BIBLIOGRAPHY	1974-Present
FEDERAL REGISTER ABSTRACTS	1977-Present
FEDERAL RESEARCH IN PROGRESS	1976-Present

FSTA (Food Science and Technology Abstracts)	1969-Present
GPO	
IPA (International Pharmaceutical Abstracts)	1970-Present
LIFE SCIENCES COLLECTION	1978-Present
METADEX	1966-Present
NTIS	1970-Present
OCCUPATIONAL SAFETY AND HEALTH	1972-Present
PTS PROMT	1972-Present
PTS F&S INDEXES	1972-Present
POLLUTION ABSTRACTS	1970-Present
SCISEARCH	1974-Present
WORLD TEXTILES	1970-Present

CIS

OHMTADS
SPHERE, CESARS, DERMAL, ENVIROFATE, GENETOX, and ISHOW

BRS

KIRK-OTHMER	1978-Present

INFOLINE

LABORATORY HAZARD BULLETIN	1981-Present
CURRENT AWARENESS IN BIOLOGICAL SCIENCES	1983-Present
CHEMICAL HAZARDS IN INDUSTRY	1984-Present
WORLD SURFACE COATING ABSTRACTS	1976-Present

OTHERS

CECATS	
CURRENT AWARENESS	
DIDS	1950-Present
EMIC	1940-Present
ETIC	
EPACASR	
ITS	
NOES	
NOHS	
NTP CHEMTRACK	
STORET	
TSCA INVENTORY	
HAZARDLINE	1983-Present
OSHA MONITORING DATA BASE	

PROJECTED NUMBERS BY INDUSTRY 01/22/86

CAS # 12108013 3 HAZ 06547 DESCRIPTION METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL

SIC CODE	DESCRIPTION	ESTIMATED PLANTS	ESTIMATED PEOPLE	ESTIMATED EXPOSURES
28	CHEMICALS AND ALLIED PRODUCTS	129	1,620 **	1,620
29	PETROLEUM AND COAL PRODUCTS	19	641 ***	641
30	RUBBER AND PLASTICS PRODUCTS, NEC	8	176 ***	176
33	PRIMARY METAL INDUSTRIES	40	2,130 ***	2,130
34	FABRICATED METAL PRODUCTS	188	3,768 ***	3,768
35	MACHINERY, EXCEPT ELECTRICAL	98	10,963 ***	10,963
36	ELECTRICAL EQUIPMENT AND SUPPLIES	27	27 ***	27
37	TRANSPORTATION EQUIPMENT	81	1,630 ***	1,630
38	INSTRUMENTS AND RELATED PRODUCTS	22	22 ***	22
39	MISCELLANEOUS MANUFACTURING INDUSTRIES	23	1,483 **	1,483
46	PIPE LINE TRANSPORTATION	11	34 ***	34
55	RETAIL GENERAL MERCHANDISE	79	474 ***	474
TOTAL		720	22,967 ***	22,967

** USE FIRST STANDARD DEVIATION COLUMN, EMPLOYEE TABLE
*** USE SECOND STANDARD DEVIATION COLUMN, EMPLOYEE TABLE

National Occupational Hazard Survey

PROJECTED NUMBERS BY OCCUPATION 01/22/80

CAS # HAZ DESCRIPTION

012108133 86567 METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL

OCC CODE	DESCRIPTION	ESTIMATED PLANTS	ESTIMATED PEOPLE	ESTIMATED EXPOSURES
095	CHEMISTS	60	114 ***	114
191	CHEMICAL TECHNICANS	152	432 ***	432
192	ENGINEERING AND SCIENCE TECHNICIANS, N.E.C.	24	47 ***	47
425	DECORATORS AND WINDOW DRESSERS	79	474 **	474
441	FOREMEN, N.E.C.	45	318 ***	318
446	HEAT TREATERS, ANNEALERS, AND TEMPERERS	134	360 **	360
461	MACHINISTS	56	1,077 ***	1,077
462	MACHINIST APPRENTICES	5	97 ***	97
481	HEAVY EQUIPMENT MECHANICS, INCL. DIESEL	5	59 ***	59
506	OPTICIANS, AND LENS GRINDERS AND POLISHERS	22	22 **	22
530	PRESSMEN AND PLATE PRINTERS, PRINTING	4	7 ***	7
585	STATIONARY ENGINEERS	19	75 ***	75
561	TOOL AND DIE MAKERS	89	3,420 ***	3,420
562	TOOL AND DIE MAKER APPRENTICES	30	261 ***	261
602	ASSEMBLERS	35	714 ***	714
610	CHECKERS, EXAMINERS, AND INSPECTORS; MANUFACT	29	275 ***	275
622	FURNACEMEN, SMELTERMEN, AND POURERS	24	919 ***	919
642	OILERS AND GREASERS, EXC. AUTO	14	14 ***	14
643	PACKERS AND WRAPPERS, EXCEPT MEAT AND PRODUCE	57	1,513 ***	1,513
644	PAINTERS, MANUFACTURED ARTICLES	47	94 ***	94
650	DRILL PRESS OPERATIVES	77	5,374 ***	5,374
651	GRINDING MACHINE OPERATIVES	24	238 ***	238
652	LATHE AND MILLING MACHINE OPERATIVES	67	2,696 ***	2,696
656	PUNCH AND STAMPING PRESS OPERATIVES	14	203 ***	203
662	SAWYERS	27	27 ***	27
680	WELDERS AND FLAME-CUTTERS	26	106 ***	106
690	MACHINE OPERATIVES, MISCELLANEOUS SPECIFIED	176	967 ***	967
692	MACHINE OPERATIVES, NOT SPECIFIED	47	1,453 ***	1,453
696	MISCELLANEOUS OPERATIVES	8	176 ***	176
695	NOT SPECIFIED OPERATIVES	26	81 **	81
706	FORK LIFT AND TOW MOTOR OPERATIVES	50	76 ***	76
753	FREIGHT AND MATERIAL HANDLERS	45	555 ***	555
903	JANITORS AND SEXTONS	14	116 ***	116
TOTAL		*	22,967 ***	22,967

* ESTIMATED PLANTS NOT ADDITIVE BY OCCUPATION
** USE FIRST STANDARD DEVIATION COLUMN, EMPLOYEE TABLE
*** USE SECOND STANDARD DEVIATION COLUMN, EMPLOYEE TABLE

NATIONAL OCCUPATIONAL EXPOSURE SURVEY AS OF: 01/23/86 PAGE 4

ESTIMATED TOTAL AND FEMALE EMPLOYEES
FIELD OBSERVATION DATA

CAS # RTECS # HAZ DESCRIPTION

0001210133 UP1950000 00597 MANGANESE, TRICARBONYL(METHYL-PI-CYCLOPENTADIENYL)-

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLYS	FEMALE EMPLYS	TOTAL EXPOS	FEMALE EXPOS
29	PETROLEUM AND COAL PRODUCTS	10	1,000		1,000	
TOTAL		10	1,000		1,000	

NATIONAL OCCUPATIONAL EXPOSURE SURVEY AS OF: 01/23/86 PAGE 4

ESTIMATED TOTAL AND FEMALE EMPLOYEES
FIELD OBSERVATION DATA

CAS # RTECS # HAZ DESCRIPTION

0001210133 UP1950000 00597 MANGANESE, TRICARBONYL(METHYL-PI-CYCLOPENTADIENYL)-

OCC CODE	DESCRIPTION	PLANTS	TOTAL EMPLYS	FEMALE EMPLYS	TOTAL EXPOS	FEMALE EXPOS
953	JANITORS AND CLEANERS	10	605		605	
756	PACKAGING AND FILLING MACHINE OPERATORS	10	68		68	
856	INDUSTRIAL TRUCK AND TRACTOR EQUIPMENT OPERATORS	10	215		215	
869	LABORERS, EXCEPT CONSTRUCTION	10	98		98	
999	NO OCC CODE AVAILABLE	10	94		94	
TOTAL			1,000		1,000	

ENCLOSURE 3
NOES

National Occupational Hazard Survey

NIOSH TRADENAME INGREDIENT DATA BASE - NOHS DATE 11/22/85 PAGE 53

84547 METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL

0219879 ETHYL CORP SPO BOX 341 SBATON ROUGE, LA 70821

0219878 COMBUSTION IMPROVER NO. 2 96 %

ENCLOSURE 4
NOHS

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